REMARKS

Status of the Claims

Claims 1-21, and 23-40 are pending and claims 18, 20-21, 23-24, 26-29, and 40 are under consideration in this application, claims 1-17, 19, 25, and 30-39 having been withdrawn for allegedly being drawn to separate inventions. All the claims under consideration stand rejected.

The dependency of claim 40 has been corrected and punctuation has been added to claim 18 for enhanced clarity. Claims 27 and 29 have been amended to further clarify antecedent bases. Claims 17 and 30-39 have been cancelled without prejudice to their being presented in a separate application. Claims 41-51 have been added and are supported by, for example, claims 18-29 as originally filed. None of the amendments made herein and none of the claims added herein add new matter.

After entry of the amendments made herein, claims 1-16, 18-21, 23-29, and 40-51 will be pending and claims 18, 20-21, 23-29, and 40-51 will be under consideration, claims 17 and 30-39 having been cancelled and claims 41-51 having been added herein.

Examiner's Clarification of the Record

From the comments on page 3, lines 1-6, of the Office Action, Applicants understand the Examiner's position to be that the animals Vallera et al. disclosed as being treated with a radiolabeled immunotoxin correspond to subjects suspected of having cancer and subsequently found not to have cancer. Applicants respectfully disagree with this position in that the animals disclosed by Vallera et al. were apparently normal and were in no way indicated to be "suspected of having cancer." Applicants submit that subjects "suspected of having cancer" (even if later shown not to have cancer) are qualitatively different from normal subjects not "suspected of having cancer" in that, in order to be "suspected of having cancer", a subject must display some symptom or sign that is at least consistent with having cancer. Vallera et al. does not disclose the presence of any such symptom or sign in the radiolabeled immunotoxin-treated animals it discloses.

35 U.S.C. § 112, second paragraph, rejection

Claim 22 stands rejected as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention.

In view of the statement on page 3, lines 14-15, of the Office Action ("Claim 24: The claim as written is confusing because it depends on canceled claim 22."), Applicants assume that it is claim 24 rather than claim 22 that the Examiner intended to reject. Applicants have amended claim 24 and, for consistency, claim 25 to be dependent on claim 18. In light of the amendment to claim 24, Applicants respectfully submit that the rejection is moot.

35 U.S.C. § 103(a) rejection

Claims 18, 20, 21, 23, 26-29, and 40 stand rejected as allegedly being unpatentable over Pastan et al.

In the statement of rejection, the Examiner cites only Pastan et al. but in the reasons for the rejection refers also to Goldenberg (at page 5, line 4, to page 6, line 2). Applicants understand from the text of the reasons for the rejection (e.g., at page 5, lines 1-15, of the Office Action) that the Examiner relies on Goldenberg for the rejection of only claims 27 and 29. Clarification is respectfully requested.

From the comments on page 4, lines 3-22, of the Office Action, Applicants understand the Examiners position to be that in disclosing the use of two component toxin-conjugated or radiolabeled single chain Fv regions for treatment and diagnosis of cancer, Pastan et al. renders obvious the methods of the instant claims involving three component molecules containing a sFv antibody fragment, a toxic domain and at least one radionuclide atom. Applicants respectfully disagree with this position. Nevertheless, in order to expedite prosecution of the instant application, Applicants have incorporated the limitations of originally filed claim 9 (specifying particular radionuclide atoms) into claim 18, deleting radionuclide atoms disclosed by Pastan et al., i.e., ^{125}I and ^{32}P (e.g., at column 9, lines 17-18, and column 19, lines 33-34). These two radionuclides have also been deleted from claim 27.

With respect to the Goldenberg reference, Applicants respectfully submit that one ordinarily skilled in the art of cancer treatment and/or diagnosis would not look to teachings relating purely to infectious diseases (such as the teachings of Goldenberg) in order to devise strategies for cancer treatment and/or diagnosis. Moreover, should such an artisan happen by chance to be aware of both the cited references, Applicants respectfully submit that neither contain disclosure that would motivate her to combine their respective disclosures and hence to conjugate the radionuclide atoms disclosed by Goldenberg to the sFv antibody fragments disclosed by Pastan et al., let alone to combine such radionuclide atoms with both sFv antibody fragments and toxic domains.

Thus, the methods of Pastan et al. relate only to cancer and the reference makes no mention of, and does not even suggest, treatment and/or diagnosis of infectious disease by any means, let alone by applying its methods to infectious diseases.

Similarly, Goldenberg is concerned only with the treatment and diagnosis of infectious diseases and does mention or even suggest the desirability of treating or diagnosing cancer by any method, let alone treating or diagnosing cancer with an immunotoxin of any sort. In addition, Goldenberg discloses the use of radiolabeled antibodies for therapy (e.g., at column 18, lines 3-47) and diagnosis (e.g., at column 12, lines 46-65) of infectious diseases and toxin-conjugated antibodies for the therapy of infectious diseases (e.g., at column 16, lines 5-34). However, the reference does not however disclose or even suggest the usefulness of the three component immunotoxins employed in the methods of the instant claims (i.e., immunotoxins containing a sFv antibody fragment, a toxic domain, and at least one radionuclide atom). In addition, the toxins that Goldenberg indicates to be useful for its purposes are those "which have a cytotoxic effect on pathogens (*sic*) microbes that may infect a human." (column 16, lines 5-7). There is no mention or even the slightest hint in Goldenberg that such toxins be active against vertebrate cancer cells, let alone that they be any of the toxins specified by the instant claims. Furthermore, Goldenberg does not mention or even hint at the use of a sFv antibody fragment at all, let alone constructing an immunotoxin containing a sFv antibody fragment and a toxin (with

or without a radionuclide), even for its own purposes, i.e., treatment and diagnosis of infectious diseases.

In view of the above-described deficiencies in the disclosures of Pastan et al. and Goldenberg, neither reference provides the necessary motivation for one ordinarily skilled in the art of cancer treatment and/or diagnosis who happens to be aware of both references to combine their respective disclosures and hence to conjugate the radionuclide atoms disclosed by Goldenberg to immunotoxins containing sFv antibody fragments and toxic domains disclosed by Pastan et al.

In addition to the above considerations, the experiments described in Example 4 of the instant application provided, for the first time, data showing that immunotoxins labeled with radionuclides are more effective than unlabeled immunotoxin at enhancing survival of animals having cancer. Thus, an ^{131}I-labeled immunotoxin (DTe23; the first 389 amino acids of diphtheria toxin linked to a sFv antibody fragment specific for erbB2) enhanced the survival of nude mice injected with human ovarian cancer cells more efficiently than unlabeled DTe23 (page 45, paragraph 2, of the specification and Fig. 9). Moreover, the survival of nude mice injected with human colon cancer cells was greater when the mice were injected with ^{64}Cu-labeled DTe23 than when injected with unlabeled DTe23 (page 46, paragraph 1, of the specification and Fig. 11). These unexpected results, obtained using two different radionuclides and two different cancers, provide further support for the non-obviousness of the methods of the present invention.

In light of all the above factors, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

In summary, for the reasons set forth above, Applicants maintain that the pending claims patentably define the invention. Applicants request that the Examiner reconsider the rejections as set forth in the Office Action, and permit the pending claims to pass to allowance.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicants' undersigned representative can be reached at the telephone number listed below.

Enclosed is a request for an automatic extension of time and a check in payment of the extension of time. Please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 09531-023001.

Respectfully submitted,

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